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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,697	KUFER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-25 and 27-57* is/are pending in the application.

4a) Of the above claim(s) *17-19,22,41-43,46 and 49-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16,20,21,23,25,27-40,44,45,47,56 and 57* is/are rejected.

7)☒ Claim(s) *24 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-25, and 27-57 are pending.

2. Claims 17-19, 22, 41-43, 46, and 49-55 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 7/20/06, the following objection and rejections remain.

4. Claims 15, 20, 39, and 44 stand objected to as the claims encompass non-elected embodiments.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-16, 20-21, 23, 25, 27-40, 44-45, 47, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated bispecific single-chain antibody comprising the amino acid sequence of SEQ NO: 1 wherein the bispecific antibody binds specifically to human CD3 and human tumor antigen EpCAM for recruiting human cytotoxic T cells to kill human EpCAM bearing cells, (2) the bispecific single chain antibody consisting of three antibody variable domains wherein the first domain is the immunoglobulin light chain CDR3 of anti-human EpCAM fused to a second domain wherein the second domain is the immunoglobulin heavy chain CDR3 of anti-human EpCAM fused to a third domain wherein the third domain is the immunoglobulin heavy chain CDR3 of anti-human CD3 via a 5 amino acid spacer of sequence Gly4Ser, **does not** reasonably provide enablement for any bispecific antibodies comprising any three antibody variable domains on a single chain as set forth in claims 1, 3-16, 20-21, 23, 25, 27-40, 44-45, 47, 56 and 57. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 1, 3-16, 20-21, 23 and 56 are broadly drawn to any bispecific single chain antibody comprising a first and second portion wherein the first portion consisting of any antibody variable domain and wherein the second portion comprising any two antibody variable domains from any antibody. The claimed antibody does not comprise all six CDRS from the heavy and light chain of the antibody or CDRs from one antibody and CDRs from another antibody.

Claims 25, 27-40, 44-45, 47 and 57 are broadly drawn to any bispecific single chain antibody comprising a first and second portion wherein the first portion comprising any two antibody variable domains and wherein the second portion consisting of any one antibody variable domains from any antibody.

The specification discloses only *one* bispecific single-chain antibody comprising the amino acid sequence of SEQ NO: 1 that binds specifically to human CD3 and human tumor antigen EpCAM for recruiting human cytotoxic T cells to kill human EpCAM bearing cells (see page 20-21.

The specification does not teach how to make any bispecific antibody as set forth in claims 1, 3-16, 20-21, 23, 25, 27-40, 44-45, 47, 56 and 57 because of the lack of guidance as to the *binding specificity* of any and all bispecific antibody. Further, there is insufficient guidance as to the structure of the variable domain in the first and second portions of the claimed bispecific antibody without the amino acid sequence. Specifically, the bispecific single chain antibody does not consist of the specific heavy chain CDR3 and light chain CDR3 of any and all antibody. It is known that CDR3 from the heavy and light chain play a critical role in antibody binding specificity and affinity. Further, the bispecific single chain antibody lacks the spatial sequence that links the first, second and third domains to maintain the critical conformation for binding.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRS which provide the majority of the contact

residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979, 1982; PTO 892).

Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Kobrin et al (J Immunology 146: 2017-2020, 1991; PTO 892) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine biding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular).

Further, the term "portion" could be as little as one amino acid. Even if the portion is limited to the antibody variable domain, there is insufficient guidance as to which domains (CDRs) from the heavy and light chain from which antibody linked to which domains (CDRs) from the heavy and light chain of another antibody without the amino acid sequence.

Barrios et al teach the length of the antibody heavy chain complementarity determining region (CDR3) is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains in the first and second portion of the claimed bispecific antibody is important in maintaining their required conformation for binding and in vivo activity.

Given the unlimited combination of first portion and second portion comprising any variable domains wherein the first and second portions are from the same or different species, there is insufficient working example showing that any combination of CDRs will maintain the three dimensional structure of an antibody and still binds specifically to human CD3 and human tumor antigen EpCAM. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that first, with regard to making, it seems that the examiner is arguing that the specification contains insufficient guidance on making when it is argued that specific operable CDRs and CDR combinations are not identified. However, it is not the only way enablement is achieved. Second, with regard to how to use, both claims 1 and 25 contain functional restrictions that exclude inoperable species, exemplified in claim 1 below: ... a first portion of the bispecific antibody is capable of recruiting the activity of a human effector cell by specifically to an effector antigen located on the human immune effector cell, said first portion consisting of one antibody variable domain; and a second portion of the bispecific antibody is capable of binding to a target antigen other than the effector antigen, said target antigen being located on a target cell other than said human immune effector cell, and said second portion comprising two antibody variable domains.

In response, amended claim 1 and dependent claims thereof are drawn to any single chain bispecific antibody comprising any three antibody variable domains wherein a first portion consisting of any antibody variable domain that binds to any effector antigen on any human immune effector cell, and a second portion comprising any two variable domains that binds to any target antigen. Amended claim 25 and dependent claims thereof are drawn to any single chain bispecific antibody comprising any three antibody variable domains wherein a first portion of the bispecific antibody comprising any two antibody variable domains that binds to any effector antigen on any human immune effector cell, and a second portion consisting of any one variable domain that binds to any target antigen. The specification does not teach how to make any bispecific antibody as set forth in claims 1, 3-16, 20-21, 23, 25, 27-40, 44-45, 47, 56 and 57

because of the lack of guidance as to the *binding specificity* of any and all bispecific antibody. Further, there is insufficient guidance as to the structure of the variable domain in the first and second portions of the claimed bispecific antibody without the amino acid sequence. Specifically, the bispecific single chain antibody does not consist of the specific heavy chain CDR3 and light chain CDR3 of any and all antibody. It is known that CDR3 from the heavy and light chain play a critical role in antibody binding specificity and affinity. Further, the bispecific single chain antibody lacks the spatial sequence that links the first, second and third domains to maintain the critical conformation for binding. At an absolute minimum, it is advantageous to use at least the third complementarity determining region (CDR) from a VH domain of such a parent antibody in designing the first and/or second portion of the bispecific antibody. This is due to the fact that the VH-CDR3 is known to play a major role in the specificity and affinity of binding of all the CDR regions, of which there are three in each of VH and VL (see specification page 12 and page 20).

With respect to the argument that one can screen any putative bispecific antibody to identify those antibody that are functional, the specification does not provide any screening method that is predictive of in vivo success for treating cancer using the claimed bispecific antibody. As such, applicants merely extend an invitation to one skilled in the art to further experimentation to arrive at the claimed invention. Given the lack of guidance as to the binding specificity of the claimed bispecific antibody and the unlimited number of bispecific antibody, it would require undue experimentation of one skilled in the art to practice the claimed invention. Even if there are

7. Claims 1, 3-16, 20-21, 23, 25, 27-40, 44-45, 47, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) binding specificity of any and all bispecific antibody, (2) the antibody variable domains (CDRs) in a first portion and (3) the antibody variable domains (CDRs) in second portion of any and all bispecific antibody.

The specification discloses only one bispecific single-chain antibody comprising the amino acid sequence of SEQ NO: 1 that binds specifically to human CD3 and human tumor

antigen EpCAM for recruiting human cytotoxic T cells to kill human EpCAM bearing cells (see page 20-21.

With the exception of the specific bispecific single chain antibody mentioned above, there is insufficient written description about the *structure*, i.e., six CDRs of heavy and light chains associated with *binding specificity* of any and all bispecific antibody without the amino acid sequence. Further, the term "portion" could be as little as one amino acid.

Even if the portion is limited to the antibody variable domain, there is inadequate written description about the two antibody variable domains (CDRs) from heavy chain (VH) and light chain (VL) in the first portion of the bispecific antibody and the two antibody variable domains (CDRs) from the heavy chain (VH) and light chain (VL) in the second portion of the bipsecific antibody without the amino acid sequence.

With regard to claims 15 and 39, there is inadequate written description about the binding specificity of the other "target antigen" to which the bispecific antibody binds. Further, there is inadequate written description about the structure of any antibody variable domains in a first and second portion without the amino acid sequence.

With regard to claims 20 and 44, there is inadequate written description about the binding specificity of the other "effector antigen" to which the bispecific antibody binds. Further, there is inadequate written description about the structure of any antibody variable domain in a first and second portion without the amino acid sequence.

With regard to claims 23 and 47, there is inadequate written description about the structure of any antibody variable domain in a first and second portion without the amino acid sequence. Further, the term "comprising" is open-ended. It expands the second portion in claim 23 and the first portion in claim 47 to include additional amino acids at either or both ends. There is inadequate written description about the amino acids to be added.

The specification discloses only one bispecific single chain antibody that binds specifically to human CD3 and EpCAM, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of compound to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that none of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known. Here, the examiner is making a similar requirement – that applicants provide a re-description of known CDRs and does so based on similar case law.

In response, every case is examiner on its own merit. Instant claims fail to describe the binding specificity of the claimed bispecific antibody. Specifically, the specific effector antigen on human immune cell and the specific target antigen on a target cell other than human immune effector cell to which the claimed bispecific antibody binds. Further, the structure, i.e., the amino acid sequence of which one antibody variable domain of the first portion and the structure of which two variable domains from which antibody in the second portion of the claimed bispecific antibody in claim 1 are not adequately described. Likewise, the structure, i.e., the amino acid sequence of which two antibody variable domains of the first portion and the structure of which one antibody variable domain in the second portion of the claimed bispecific antibody in claim 25 are not adequately described. Every antibody is unique in terms of binding specificity and its six CDRs from immunoglobulin heavy and light chains. Without the sequence of CDRs and the linkers that link the various domains to maintain the spatial conformation of the CDRs for binding, Applicants merely ask one of skill in the art to come up with the structure and the binding specificity of the claimed bispecific antibody.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3, 5, 7-8, 13-16, 20-21, 23, 25, 27-29, 31-32, 37-40, 44-45, and 47 stand rejected under 35 U.S.C. 102(b) as being anticipated by Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 1449).

Mack et al teach a bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 comprising two antibody variable domains on a single polypeptide chain comprising a first portion such as VH-VL that binds specifically to effector antigen such as CD3 expressed on human Jurkat T cells or human PMBCs and a second portion comprising two antibody variable domains such as VL-VH that binds specifically to a target antigen such as 17-1A (EpCAM) located on target tumor cells such as Kato cells or X63 plasmacytoma cells (see page 7022, Fig 1, Materials and Methods, page 7023, col. 2, Binding properties, in particular). The reference first portion and the second portion are from the same species such as mouse and independently derived from two mouse hybridomas (see M79 hybridoma and TR66 hybridoma on page 7021, Col. 2, Materials and Methods, in particular). The reference mouse derived first and second portions are variable domain from heavy chain (VH) (see Figure 1, in particular). The reference human effector cell such as PMBCs or Jurkat T cells are member of the human lymphoid lineage of CD3 positive T cells that exert cytotoxic effect on tumor cells (see Figs 5-6, page 7024, in particular). The binding of the first portion of the bispecific antibody to human CD3 positive T cells is capable of recruiting the activity of human effector T cells such as cytotoxic T cells to the target tumor cells expressing EpCAM (see abstract, in particular). The term "comprising" in claim 1 expands the second portion of the antibody variable domain to include additional amino acids at either or both ends such as Flag or linker or additional variable domain (see page 7022, Figure, col. 2, in particular). The term "comprising" in claim 25 expands the first portion of the bispecific antibody to include additional amino acids at either or both ends such as linker peptide Gly4Ser1 or (Gly1Ser1)3 and His (see page 7022, Figure, col. 2, in particular). Mack et al further teach the low molecular mass of the small bispecific single-chain antibody facilitates penetration into tumors (see page 7025, col. 1, first full paragraph, in particular) and bispecific single chain antibody is effective in redirecting human peripheral T lymphocytes against EpCAM positive tumor cells (see abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al.

10. Claims 1, 3, 5, 7-8, 11-16, 20-21, 23, 25, 27-29, 31-32, 35-40, 44-45, and 47 stand rejected under 35 U.S.C. 102(b) as being anticipated by Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449).

Mack et al teach a bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 comprising two antibody variable domains on a single polypeptide chain comprising a first portion such as VH-VL that binds specifically to effector antigen such as CD3 expressed on human Jurkat T cells or human PMBCs and a second portion comprising two antibody variable domains such as VL-VH that binds specifically to a target antigen such as 17-1A (EpCAM) located on target tumor cells (see page 3966, Fig 1, Production of bispecific single-chain Ab, in particular). The reference the first portion is derived from mouse hybridoma TR66 and the second portion is derived from mouse hybridoma M79 which is the same species (see page 3966, col. 1, Production of the bispecific single chain Ab, in particular). The reference first and second portion are independently derived from two different mouse hybridomas (see page 3966, col. 1, Production of the bispecific single chain Ab, in particular). The reference mouse derived first and second portions are variable domains from heavy chain (VH) and light chain (VL) (see Figure 1 on page 3966, in particular). The term "comprising" in claim 1 expands the second portion of the antibody variable domain to include additional amino acids at either or both ends such as Flag or linker (see Figure 1 at page 3966, col. 1, in particular). The term "comprising" in claim 25 expands the first portion of the bispecific antibody to include additional amino acids at either or both ends such as linker peptide Gly4Ser1 or (Gly1Ser1)3 and His (see Figure 1, in particular). The reference human effector CD3 positive cell cells are PMBCs, CD4+ or CD8+ T cells which are member of the human lymphoid lineage of CD3 positive T cells that exert cytotoxic effect on tumor cells (see page 3966, col. 1, Preparation of Effector cells, page 3966, col. 2, cytotoxicity assay, Figures 5-6, in particular). The binding of the first portion of the bispecific antibody to human CD3 positive T cells is capable of recruiting the activity of human effector T cells such as cytotoxic T cells to the target tumor cells such as human Kato cells expressing the EpCAM antigen or mouse X63 cell expressing the EpCAM (see caption of Figure 5 and 6, in particular). The reference further teaches the immunogenicity of the reference bispecific Ab construct could

be reduced further by humanization i.e. insertion of hypervariable region from the heavy and light chain of mouse mAb reactive with 17-1A (EpCAM) and CD3 into a human IgG to prevent the formation of human anti-mouse Abs (see page 3970, col. 1, in particular). Mack et al teach the advantage in the use of small bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 is that it redirect cytotoxic T cells to tumor cells in an MHC-unrestricted fashion; its remarkable stability at 37 °C in serum and the lack of immunogenicity of the Fc region allow the administration of higher does for tissue penetration as well as for optimal tumor killing (see page 3970, col. 1, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 4-6, 11-12, 25, 29, and 35-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 1449) in view of US 5,658,570 (Aug 1997; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claim 4 differs from the teachings of the reference only in that bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from different species.

The invention in claims 5, and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *first* portion is derived from primate.

The invention in claim 11 differs from the teachings of the reference only in that the bispecific antibody has undergone an alteration to render it less immunogenic when administered to humans.

The invention in claims 12 and 36 differs from the teachings of the reference only in that the bispecific antibody has undergone chimerization or framework amino acids to correspond to the closet human germline sequence to render it less immunogenic when administered to humans.

The '570 patent teaches chimeric antibody that binds specifically to human CD3 (see entire document, claims 1-8, in particular). The reference chimeric antibody comprises CDRs from the heavy and light chain (VL) and (VH) of Old World Monkey and immunoglobulin framework region from human (see col. 5, lines 21-33, in particular) or human constant region. The CDR grafted antibody is able to bind to the same antigen as the original monkey antibody (see col. 5, lines 29-30, in particular). The '570 patent also teaches mutation of framework amino acids to correspond to the closet human germline sequence (see col. 5, lines 39-65, in particular). The '570 patent teaches the monkey, chimpanzee and human variable region leader sequences are quite similar and few differences in the amino acid sequence of human and chimpanzee constant region that an antibody be produced with less immunogenicity (see col. 3, lines 47 bridging col. 4, lines 1-17, in particular). The advantage in the use of humanized or chimerized antibody is that the immune response to certain murine sequence could be further reduced or eliminated by their substitution with primate or human sequence since the chimpanzee and human variable region leader sequences are quite similar and the problem of induction of human anti-antibody (HAA) upon repeated administration necessary to treat chronic conditions could be circumvented (see col. 2, lines 26-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to human CD3 in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to human CD3 that derived from primate as taught by the '570 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantage in the use of humanized or chimerized antibody is that the immune response to certain murine sequence could be further reduced or eliminated by their substitution with primate or human sequence since the chimpanzee and human variable region leader sequences are quite similar and the problem of induction of human anti-antibody (HAA) upon repeated administration necessary to treat chronic conditions could be circumvented as taught by the '570 patent (see col. 2, lines 26-45, in particular). Mack et al teach the low molecular mass of the small bispecific single-chain antibody facilitates penetration into tumors (see page 7025, col. 1, first full paragraph, in particular) and bispecific single chain antibody is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells (see abstract, in particular).

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. The motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors (see page 7025, col. 1, first full paragraph, in particular) and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

14. Claims 1, 4-6, 25, and 29-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 1449) in view of WO 98/46645 publication (Oct 1998; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claim 4 differs from the teachings of the reference only in that bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from different species.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *second* portion is derived from primate.

The invention in claims 6 and 30 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *second* portion is derived from man.

The WO 98/46645 publication teaches various human antibodies such as single chain, chimerized antibodies and binding fragment that bind to human tumor antigen 17-1A, also known as EpCAM, EGP, GA 733-2 (see abstract, claims of 18-33 of WO 98/46645, in particular). One of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans (see page 13, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the second portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to tumor antigen 17-A-1A (EpCAM) in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human immunoglobulin heavy and light chain that bind specifically to human tumor antigen 17-A-1A (EpCAM) that derived from human as taught by the WO 98/46645 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because one of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans as taught by the WO 98/46645 publication (see page 13, 3rd paragraph, in particular). Mack et al teach the low molecular mass of the small bispecific single-chain antibody facilitates penetration into and bispecific single chain antibody is effective in redirecting

human peripheral T lymphocytes against Ep-ICAM positive tumor cells (see abstract, in particular).

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. The motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

15. Claims 1, 5-6, 25, and 27-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 1449) in view of WO 98/46645 publication (Oct 1998; PTO 892) and US Pat No. 5,849,288 (Dec 1998; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claims 3, and 27-28 differs from the teachings of the reference only in that bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from the same species.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *first* and *second* portions are derived from primate.

The invention in claims 6 and 30 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *first* and *second* portions are derived from man.

The WO 98/46645 publication teaches various human antibodies such as single chain, chimerized antibodies and binding fragment that bind to human tumor antigen 17-1A, also known as EpCAM, EGP, GA 733-2 (see abstract, claims of 18-33 of WO 98/46645, in particular). One

of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans (see page 13, 3rd paragraph of WO98/46645, in particular). The '288 patent teaches commercially useful amounts of human antibody can easily be produced in chimeric mouse having hematopoietic cells from human donor (see summary of invention, col. 4, lies 7-14, in particular).

The '288 patent teaches a method of making human antibodies to any antigen of interest such as human CD3 using mouse or rat having human xenogenic hematopoietic cells (see entire document, summary of invention, col. 21, lines 58 through col. 22, col. 24, lines 35, col. 28, line 46-51, claims of '288 patent, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first portion that bind specifically to human CD3 in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human antibody that binds to human CD3 as taught by the '288 patent and then substitute the second portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to tumor antigen 17-A-1A (EpCAM) in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human immunoglobulin heavy and light chain that bind specifically to human tumor antigen 17-A-1A (EpCAM) that derived from human as taught by the WO 98/46645 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because one of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans as taught by the WO 98/46645 publication (see page 13, 3rd paragraph, in particular). The '288 patent teaches commercially useful amounts of human antibody can easily be produced in chimeric mouse having hematopoietic cells from human donor (see summary of invention, col. 4, lies 7-14, in particular). Mack et al teach the low molecular mass of the small bispecific single-chain antibody facilitates penetration into tumors (see page 7025, col. 1, first full paragraph, in particular) and bispecific single chain antibody is effective in redirecting human peripheral T lymphocytes against Ep-ICAM positive tumor cells (see abstract, in particular).

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. The motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

16. Claims 1, 5, 9-10, 25, 29, and 33-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 1449) in view of Frenken et al, J Biotechnology 78: 11-21, 2000; PTO 892) and Muyldermans et al (J Molecular Recognition 12: 131-140, 1999; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody wherein the first and second portion is derived from tylopoda or cartilaginous fish.

The invention in claims 9 and 33 differs from the teachings of the reference only in that the bispecific antibody wherein the tylopoda-derived first and second portion are derived from camel, llama or dromedary.

The invention in claim 10 and 34 differs from the teachings of the reference only in that the bispecific antibody wherein camel, llama or dromedary derived first and second portion is a VHH domain.

Frenken et al teach a method of making antibody or immunoglobulin that binds to any antigen from *Camelidae* such as camel, llama or dromedary. The method includes the steps of immunizing the llama with the antigen of interest, obtaining antigen specific heavy chain (VHH) and producing these VHH domain in yeast *Saccharomyces cerevisiae* (see entire document, abstract, page 12, material and methods, page 14, paragraph bridging col. 1 and col. 2, in particular). The advantage in the use of VHH domain is that the binding affinity and specificity

for the antigen of VHH is similar to Fab fragment derived form a mouse monoclonal antibody, the antigen specific llama VHH fragment is extremely temperature stable, and could easily be secreted by S. cervisiase since the molecular weight and size of the VHH domains is about half that of a scFv fragment (see page 19-20, abstract, in particular).

Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). Natural occurring antibody binding portion such as VHH (single domain) heavy chain antibody isolated from camels, or llamas is the smallest antigen binding fragment (see page 132, col. 2, Figure 1B-C, in particular). Muyldermans et al further teach antibody from nurse shark (cartilaginous fish) also composes of one V domain followed by five constant domains analogous to the bona fide camelid heavy-chain antibodies (see paragraph bridging page 132 and 133, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make any antibody VHH domains from camel, llama or dromedary as taught by Frenken et al or cartilaginous fish as taught by Muyldermans et al that binds specifically to CD3 and 17-1A (EpCAM) as taught by Mack et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantage in the use of VHH domain is that the binding affinity and specificity for the antigen of VHH is similar to Fab fragment derived form a mouse monoclonal antibody, the antigen specific llama VHH fragment is extremely temperature stable, and could easily be produced by *S. cervisiase* since the molecular weight and size of the VHH domains is about half that of a scFv fragment as taught by Frenken et al (see page 19-20, abstract, in particular). Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). Mack et al teach the low molecular mass of the small bispecific single-chain antibody facilitates penetration into tumors (see page 7025, col. 1, first full paragraph, in particular) and bispecific single chain antibody is effective in

redirecting human peripheral T lymphocytes against Ep-ICAM positive tumor cells (see abstract, in particular).

Applicants' arguments filed 7/20/06 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, the motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular). Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular).

17. Claims 1, 4-6, 11-12, 25, 29, and 35-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449) in view of US 5,658,570 (Aug 1997; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claim 4 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from different species.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion is derived from primate.

The invention in claims 12 and 36 differs from the teachings of the reference only in that the bispecific antibody has undergone chimerization or framework amino acids to correspond to the closet human germline sequence to render it less immunogenic when administered to humans.

The '570 patent teaches chimeric antibody that binds specifically to human CD3 (see entire document, claims 1-8, in particular). The reference chimeric antibody comprises CDRs from the heavy and light chain (VL) and (VH) of Old World Monkey and immunoglobulin framework region from human (see col. 5, lines 21-33; in particular) or human constant region. The CDR grafted antibody is able to bind to the same antigen as the original monkey antibody (see col. 5, lines 29-30, in particular). The '570 patent also teaches mutation of framework amino acids to correspond to the closet human germline sequence (see col. 5, lines 39-65, in particular). The '570 patent teaches the monkey, chimpanzee and human variable region leader sequences are quite similar and few differences in the amino acid sequence of human and chimpanzee constant region that an antibody be produced with less immunogenicity (see col. 3, lines 47 bridging col. 4, lines 1-17, in particular). The advantage in the use of humanized or chimerized antibody is that the immune response to certain murine sequence could be further reduced or eliminated by their substitution with primate or human sequence since the chimpanzee and human variable region leader sequences are quite similar and the problem of induction of human anti-antibody (HAA) upon repeated administration necessary to treat chronic conditions could be circumvented (see col. 2, lines 26-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to human CD3 in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to human CD3 that derived from primate as taught by the '570 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantage in the use of humanized or chimerized antibody is that the immune response to certain murine sequence could be further reduced or eliminated by their substitution with primate or human sequence since the chimpanzee and human variable region leader sequences are quite similar and the problem of induction of human anti-antibody (HAA) upon repeated administration necessary to treat chronic conditions could be circumvented as taught by the '570 patent (see col.

2, lines 26-45, in particular). Mack et al teach the advantage in the use of small bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 is that it redirect cytotoxic T cells to tumor cells in an MHC-unrestricted fashion; its remarkable stability at 37 °C in serum allow the administration of higher does for tissue penetration as well as for optimal tumor killing (see page 3970, col. 1, in particular).

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, the motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

18. Claims 1, 4-6, 25, and 29-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449) in view of WO 98/46645 publication (Oct 1998; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claim 4 differs from the teachings of the reference only in that bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from different species.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *second* portion is derived from primate.

The invention in claims 6 and 30 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *second* portion is derived from man.

The WO 98/46645 publication teaches various human antibodies such as single chain, chimerized antibodies and binding fragment that bind to human tumor antigen 17-1A, also known as EpCAM, EGP, GA 733-2 (see abstract, claims of 18-33 of WO 98/46645, in particular). One of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans (see page 13, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the second portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind specifically to tumor antigen 17-A-1A (EpCAM) in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human immunoglobulin heavy and light chain that bind specifically to human tumor antigen 17-A-1A (EpCAM) that derived from human as taught by the WO 98/46645 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because one of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans as taught by the WO 98/46645 publication (see page 13, 3rd paragraph, in particular). Mack et al teach the advantage in the use of small bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 is that it redirect cytotoxic T cells to tumor cells in an MHC-unrestricted fashion; its remarkable stability at 37 °C in serum allow the administration of higher does for tissue penetration as well as for optimal tumor killing (see page 3970, col. 1, in particular).

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, the motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T

lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

19. Claims 1, 5-6, 25, and 27-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449) in view of WO 98/46645 publication (Oct 1998; PTO 892) and US Pat No. 5,849,288 (Dec 1998; PTO 892).

The teachings of Mack et al have been discussed supra.

The invention in claims 3, and 27-28 differs from the teachings of the reference only in that bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the first portion and the second portion are derived from the same species.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *first* and *second* portions are derived from primate.

The invention in claims 6 and 30 differs from the teachings of the reference only in that the bispecific antibody comprising two antibody variable domains on a single polypeptide wherein the *first* and *second* portions are derived from man.

The WO 98/46645 publication teaches various human antibodies such as single chain, chimerized antibodies and binding fragment that bind to human tumor antigen 17-1A, also known as EpCAM, EGP, GA 733-2 (see abstract, claims of 18-33 of WO 98/46645, in particular). One of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans (see page 13, 3rd paragraph, in particular).

The '288 patent teaches a method of making human antibodies to any antigen of interest such as human CD3 using mouse or rat having human xenogenic hematopoietic cells (see entire document, summary of invention, col. 21, lines 58 through col. 22, col. 24, lines 35, col. 28, line 46-51, claims of '288 patent, in particular). The '288 patent teaches commercially useful amounts of human antibody can easily be produced in chimeric mouse having hematopoietic cells from human donor (see summary of invention, col. 4, lies 7-14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the first portion that bind specifically to human CD3 in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human antibody that binds to human CD3 as taught by the '288 patent and then substitute the second portion such as VH-VL or CDRs from immunoglobulin heavy and light chain that bind

specifically to tumor antigen 17-A-1A (EpCAM) in the bispecific single chain antibody as taught by Mack et al for the VH-VL or CDRs from the human immunoglobulin heavy and light chain that bind specifically to human tumor antigen 17-A-1A (EpCAM) that derived from human as taught by the WO 98/46645 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because one of the advantages of human antibody is that the antibody has low or no immunogenicity when administering to humans as taught by the WO 98/46645 publication (see page 13, 3rd paragraph, in particular). The '288 patent teaches commercially useful amounts of human antibody can easily be produced in chimeric mouse having hematopoietic cells from human donor (see summary of invention, col. 4, lies 7-14, in particular). Mack et al teach the advantage in the use of small bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 is that it redirect cytotoxic T cells to tumor cells in an MHC-unrestricted fashion; its remarkable stability at 37 °C in serum allow the administration of higher does for tissue penetration as well as for optimal tumor killing (see page 3970, col. 1, in particular).

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, amended claims 1 and 25 doe not recite bispecific single chain antibody as argued. The motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

20. Claims 1, 5, 9-10, 25, 29, and 33-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449) in view of Frenken et al, J Biotechnology 78: 11-21, 2000; PTO 892) and Muyldermans et al (J Molecular Recognition 12: 131-140, 1999; PTO 892).

The combined teachings of Mack et al have been discussed supra.

The invention in claims 5 and 29 differs from the teachings of the reference only in that the bispecific antibody wherein the first and second portion is derived from tylopoda or cartilaginous fish.

The invention in claims 9 and 33 differs from the teachings of the reference only in that the bispecific antibody wherein the tylopoda-derived first and second portion are derived from camel, llama or dromedary.

The invention in claim 10 and 34 differs from the teachings of the reference only in that the bispecific antibody wherein camel, llama or dromedary derived first and second portion is a VHH domain.

Frenken et al teach a method of making antibody or immunoglobulin that binds to any antigen from *Camelidae* such as camel, llama or dromedary. The method includes the steps of immunizing the llama with the antigen of interest, obtaining antigen specific heavy chain (VHH) and producing these VHH domain in yeast *Saccharomyces cerevisiae* (see entire document, abstract, page 12, material and methods, page 14, paragraph bridging col. 1 and col. 2, in particular). The advantage in the use of VHH domain is that the binding affinity and specificity for the antigen of VHH is similar to Fab fragment derived form a mouse monoclonal antibody, the antigen specific llama VHH fragment is extremely temperature stable, and could easily be secreted by S. cervisiase since the molecular weight and size of the VHH domains is about half that of a scFv fragment (see page 19-20, abstract, in particular).

Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). Natural occurring antibody binding portion such as VHH (single domain) heavy chain antibody isolated from camels, llamas is the smallest antigen binding fragment (see page 132, col. 2, Figure 1B-C, in particular). Muyldermans et al further teach antibody from nurse shark (cartilaginous fish) also

composes of one V domain followed by five constant domains analogous to the bona fide camelid heavy-chain antibodies (see paragraph bridging page 132 and 133, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make any antibody VHH domains from camel, llama or dromedary as taught by Frenken et al or cartilaginous fish as taught by Muyldermans et al that binds specifically to CD3 and 17-1A (EpCAM) as taught by Mack et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the advantage in the use of VHH domain is that the binding affinity and specificity for the antigen of VHH is similar to Fab fragment derived form a mouse monoclonal antibody, the antigen specific llama VHH fragment is extremely temperature stable, and could easily be produced by *S. cervisiase* since the molecular weight and size of the VHH domains is about half that of a scFv fragment as taught by Frenken et al (see page 19-20, abstract, in particular). Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). Mack et al teach the advantage in the use of small bispecific single chain antibody directed against 17-1A (EpCAM) and CD3 is that it redirect cytotoxic T cells to tumor cells in an MHC-unrestricted fashion; its remarkable stability at 37 °C in serum allow the administration of higher does for tissue penetration as well as for optimal tumor killing (see page 3970, col. 1, in particular).

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, the motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T

lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

21. Claims 1, 25, 56 and 57 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 892) or Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449) each in view of U.S. Pat No. 5,858,682 (filed Aug 1996, PTO 892).

The teachings of Mack et al references have been discussed supra.

The invention in claims 56 and 57 differs from the teachings of the references only in that a kit comprising the bispecific antibody of claim 1 or claim 25.

The '682 patent teaches a kit (article of manufacture) comprising an antibody for diagnostic assays (See column 3, line 40; column 6, line 17; column 8, line 36, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by the '682 for the bispecific antibody comprising two variable antibody variable domains on a single polypeptide comprising a first portion that binds specifically human CD3 capable of recruiting human T cells and a second portion that binds specifically to target antigen EpCAM on tumor cells that is useful against residual cancer cells as taught by Mack et al (Proc Natl Acad Sci 92: 7021-7025, July 1995; PTO 892) or Mack et al (J Immunology 158: 3965-3970, 1997; PTO 1449). One would have been motivated, with a reasonable expectation of success, to place the antibody taught by Mack et al in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

Applicants' position is that amended claims 1 and 25 related to a bispecific antibody with a total of three antibody variable domains: one variable domain binds to an effector antigen on the human effector cells, whereas the other two variable domains bind to the target antigen on a

target cell. The reference describes a bispecific single chain antibody with four variable domains. The cited references actually teach away from generating a 3-domain bispecific antibody.

In response, the term "comprising" in amended claims 1 and 25 is open ended. It expands the claimed bispecific antibody to include additional variable domain such as four variable domains bispecific single chain antibody as taught by Mack et al. Further, the motivation to make a single chain bispecific antibody is that the small bispecific single-chain antibody facilitates penetration into tumors and is effective in redirecting human peripheral T lymphocytes against Ep-CAM positive tumor cells as taught by Mack et al (see abstract, in particular).

22. Claims 24 and 48 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

23. The following new ground of objection is necessitated by the amendment filed 7/20/06.

24. Claims 56-57 are objected to because "of" is recited twice in said claims.

25. No claim is allowed.

26. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The

examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

28. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 29, 2006

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